

**Windham, G.C. (1994). Developmental and reproductive effects of exposure to environmental tobacco smoke exposure, California Department of Health Services.**

**EXECUTIVE SUMMARY**

This chapter provides an evaluation of the evidence regarding the causal association between exposure to environmental tobacco smoke (ETS) and adverse developmental and reproductive outcomes. Developmental endpoints examined include both perinatal and postnatal manifestations: effects on fetal growth, spontaneous abortion and perinatal mortality, congenital malformations (birth defects), Sudden Infant Death Syndrome (SIDS), cognition and behavior, and postnatal physical development. Reproductive endpoints examined include female fertility, fecundability, and early menopause; no data on male reproductive effects were found. Effects such as childhood asthma and middle ear inflammation (otitis media) are also considered to be developmental effects; these endpoints are addressed in the draft chapter entitled: *Respiratory Health Effects of Exposure to Environmental Tobacco Smoke*.

For the purposes of the review of developmental effects, “ETS exposure” is defined as exposure to secondhand tobacco smoke experienced by the mother during pregnancy or by the child after birth. The effects of active maternal smoking during pregnancy are mentioned only for comparison. In the examination of all endpoints, data from animal studies are reviewed briefly but are not emphasized, because animal models for ETS exposure have only recently come into use. The existing data from these models pertinent to the evaluation of ETS exposure are reviewed.

The evidence provided by studies reviewed for each endpoint is characterized using the following eight-of-evidence categories: sufficient, suggestive, inadequate, or null (see Section 2.4 for definitions).

**Perinatal Manifestations**

*Fetal Growth*

More than twenty epidemiologic studies of the relationship between fetal growth and ETS exposure have been reviewed. All but one of the studies that examined mean birth weight have shown a decrement with ETS exposure, although some of the weight differences were quite small. A few early studies found little effect, but none of them controlled for confounders or performed rigorous statistical analyses. The majority of studies which examined the endpoints low birth weight or small for gestational age have shown a slightly elevated risk (20-40%) with ETS exposure. Current epidemiologic studies, with support from animal studies, provide sufficient evidence that ETS exposure adversely affects fetal growth. The primary effect is a reduction in birth weight that is of a small magnitude (25-50 grams), and may not be clinically significant for an individual infant at low risk. Yet, if the entire birth weight distribution is shifted lower with ETS exposure, as it appears to be with active smoking, infants who are already compromised may be pushed into even higher risk categories. Low birth weight is associated with many well-recognized problems for infants and is strongly associated with perinatal mortality.

### *Spontaneous Abortion and Perinatal Mortality*

Of the relatively few studies that have examined the association of ETS exposure and perinatal death, early studies suggest an increased risk of neonatal mortality rates associated with paternal smoking. The data with respect to stillbirth are more sparse, but are not indicative of an association. Two recent studies reported an association of spontaneous abortion and ETS exposure from multiple sources, although in one study the association was observed only with workplace, not home, exposure. These, as well as two weaker studies, provide some epidemiologic evidence that ETS exposure may play a role in the etiology of spontaneous abortion, but further work is needed.

### Congenital Malformations

Although the epidemiologic studies reviewed suggest a moderate association of severe congenital malformations (birth defects) with paternal smoking, none presented compelling evidence that ETS exposure causes congenital malformations. The use of paternal smoking status as a surrogate for ETS exposure means that a direct effect of active smoking on the sperm cannot be ruled out. Several studies found associations with specific defects, but the defects implicated differed in different studies. The most consistent association appears to be with central nervous system or neural tube defects; this association was observed in all but one of the five studies that provided sufficient data. Due to the exposure assessment limitations of existing studies, the data are inadequate to determine whether there is an association of ETS exposure with birth defects.

### Postnatal Manifestations

#### *Sudden Infant Death Syndrome (SIDS)*

Interest in Sudden Infant Death Syndrome (SIDS) stems from numerous studies demonstrating that infants of smoking mothers have an increased risk of SIDS. There is adequate epidemiological evidence of a causal relationship between maternal smoking in general and risk of SIDS. In most of the studies examining the relationship between ETS exposure and SIDS, it was not possible to separate the effects of postnatal ETS exposure from those of prenatal exposure to maternal active smoking. Recent findings of an elevated risk of SIDS associated with postnatal ETS exposure independent of maternal smoking in two reasonably well-controlled studies provide strong evidence that postnatal ETS exposure of the child is an independent risk factor for SIDS. However, to firmly establish a causal relationship between postnatal ETS exposure and SIDS, further research is needed to address the main limitations of the existing studies; thus, the evidence is suggestive.

#### *Cognition and Behavior*

Although studies have shown fairly consistently that maternal smoking during pregnancy is adversely associated with measures of cognition and behavior in children, very few studies have examined these effects in relation to children's postnatal ETS exposure. One study of behavior

which did a reasonably good job of separating postnatal from *in utero* exposure and controlled for other pertinent covariates found significant adverse relationships associated with childhood ETS exposure. With respect to cognitive development, the best controlled study showed no association with postnatal ETS exposure, but three other fairly well-controlled studies showed modest decrements associated with postnatal ETS exposure. A single small study of nonsmoking pregnant women found an association of ETS exposure during pregnancy with decrements in their offspring's test scores. While conclusions regarding causality cannot be made on the basis of these studies, they do provide suggestive evidence that ETS exposure may pose a neuropsychological developmental hazard.

### *Postnatal Physical Development*

While small but consistent effects of active maternal smoking during pregnancy on physical growth of offspring have been demonstrated in a number of studies, there is no epidemiological evidence that postnatal ETS exposure has a significant effect on the height growth of children after controlling for prenatal exposure to maternal active smoking. Although a relatively small number of studies have addressed this issue, to date the evidence that postnatal ETS exposure is an independent hazard to height growth in humans is difficult to characterize but is judged to be null.

### Female and Male Reproductive Toxicity

#### *Female Fertility and Fecundability*

Though active smoking by women has been found to be associated with decreased fertility in a number of studies, and tobacco smoke appears to be anti-estrogenic, the epidemiologic data on ETS exposure and reduced fertility are not extensive and show mixed results. A well-controlled study in the U.S. found no association of conception delays with spousal smoking habits, contrary to the results of two Scandinavian studies which found slight increases in conception delays but were potentially more biased studies. Because ETS exposure is defined as spousal smoking in all these studies, any association seen may be due to direct effects of active paternal smoking on male reproductive parameters. Two studies have found an association between ETS exposure during childhood and increased fecundability (in adulthood); a third study did not confirm these findings. All three studies are constrained by lack of information on potential confounders related to childhood ETS exposure. Thus, it is not possible to determine from the conflicting epidemiologic studies conducted to date whether or not ETS exposure is associated with changes in female fertility or fecundability, so the evidence for such effects is *inadequate*.

#### *Other Female Reproductive Effects*

One study found a strong association of early menopause with ETS exposure, which is consistent with findings of early menopause among active smokers. In addition, a Slovak study reported a slight, nonsignificant decrease in age at menopause. Because the analytic methods of these two studies could not be thoroughly evaluated, more studies are needed to confirm this finding. While the effect is biologically plausible, at present the evidence for effects of ETS exposure on lowered age at menopause or other measures of female reproductive dysfunction is *inadequate*.

### *Male Reproductive Effects*

No epidemiologic or animal studies were found which investigated the association of ETS exposure and male reproductive parameters. Associations have been seen in human studies of active smoking and sperm parameters. At present, the evidence is *inadequate* with respect to effects of ETS exposure on male reproductive dysfunction.

### Developmental and reproductive Toxicity of Selected ETS Components

Of the known ETS constituents, five were reviewed, three are recognized by the State of California to be developmental toxicants (nicotine, carbon monoxide and toluene); two agents have been investigated as possible mediators of the developmental or reproductive toxicity of tobacco smoke (cadmium and polycyclic aromatic hydrocarbons (PAHs)). The presence in ETS of agents that can produce, in isolation, effects similar to those that are associated with ETS exposure in epidemiological investigations provides biological plausibility for the developmental or reproductive toxicity associated with ETS exposure.

With respect to fetal growth parameters, nicotine has consistently been shown in animal studies to decrease birth weight, independent of experimental species, route of administration, maternal toxicity or endpoint studied. Carbon monoxide is a recognized developmental toxicant in several species of animals, with effects that include decreased fetal weight and increased fetal loss. In animals, toluene has been demonstrated to cause retarded intrauterine development resulting in low mean fetal weights. Animal studies of cadmium exposure indicate reduced fetal or birth weight in several species of animals. ETS contains many constituents beyond these five, however, and the contribution of any specific constituent to the overall effects of ETS exposure is not yet established.

### Conclusion

In summary, the epidemiologic evidence indicates that ETS exposure adversely affects development, with the strongest evidence for an effect on lowered birth weight. Suggestive evidence exists for effects on SIDS, and cognition and behavior. The biological plausibility of these effects is supported by an additional data, including the effects seen with active smoking, the results of animal studies of these endpoints, and the effects of exposure to selected ETS constituents. Thus the evidence is sufficient to implicate ETS exposure as a cause of developmental toxicity. Further evidence of developmental toxicity of ETS exposure is provided in chapter 5, which reviews respiratory outcomes in children. The evidence for female and male reproductive effects is inconclusive.